SUMMARY REPORT
FOR PUBLICATION

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TITLE: Surface Modification of Biomaterials for Biomedical Devices

PROJECT COORDINATOR: Patrick T. Cahalan

PARTNERS: BAKKEN RESEARCH CENTER (BRC)
RLJKSUNIVERSITY LIMBURG (RL)
CENTER FOR SURFACE AND MATERIALS ANALYSIS (CSMA)

REFERENCE PERIOD FROM: 1/11/92 to 1/11/95

STARTING DATE: 1/11/92 **DURATION: 36 MONTHS**

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BE 5972 SUMMARY REPORT

2. *TITLE*

SURFACE MODIFICATION OF BIOMATERIALS FOR USE IN BIOMEDICAL DEVICES

3. *PARTNERSHIP*

BRC - Bakken Research Center, Maastricht, The Netherlands

RL - Rijksuniversity of Limburg, University of Maastricht, Maastricht, The Netherlands

CSMA - Center for Surface and Materials Analysis, Manchester, England

4. *OBJECTIVES*

The objectives of this project were to take a broad approach to the processes for surface modification of common biomaterials in order to acquire a comprehensive capability that would permit modification of most materials used in biomedical devices. Emphasis was placed on processes that had manufacturing feasibility, and a goal of at least two devices modified and approved for human implant was set.

5. *TECHNICAL DESCRIPTION*

Seven common polymeric biomaterials used in biomedical devices manufactured by Medtronic were screened for the ability to modify the surfaces with physical and chemical methods. The methods investigated were: (Physical) irradiation, plasma, corona, CVD, PVD, SMA (blooming agents), and direct simple coating techniques: (Chemical) oxidation, reduction, hydrolysis, addition/substitution, grafting. photocoupling, and ozonization. Intermediate chemistries were used in cases where biologically active molecules were attached to the modified surfaces.

Thorough characterization of the impact of processes on the materials were carried out by CSMA using XPS and TofSIMS. Additionally staining techniques, FTIR, SEM, UV-VIS, HPLC, and mechanical testing were used to further characterize processes and surfaces.

The University of Maastricht carried out further test developments to measure bioactivity of surfaces with immobilized biomolecules, and performed blood testing to assess the blood compatibility properties of surfaces.

Successful techniques were developed and applied to devices and evaluated again with the above mentioned, techniques. Biocompatibility testing was performed by GLP approved test houses on the two devices that were selected for human clinical trials.

6. *Results and conclusions*

By previous agreement of the consortium all methods developed and applicable for biomedical devices remain the property of the BRC. RL and CSMA were encouraged to and have published several articles on results.

With respect to the final goals of two devices for human clinical trials; these were realized in the approval for human clinical trials of a wound dressing, and an intravascular stent used in conjunction with Percutaneous Translumenal Coronary Angioplasty (PTCA). In the first case a surface modification was developed to enhance the binding of b-FGF to a surface to promote more rapid and complete wound healing. In the second case heparin was covalently coupled to a tantalum coronary stent to improve the blood compatibility of this device.

Key accomplishments in addition to the goals are:

6.1 Proprietary processes for attachment of heparin to all materials and devices.
6.2 State of the art analytical methods for analysis of heparin activity on surfaces.
6.3 Publications on advanced understanding of the mechanism of improvement of blood compatibility by a heparinized surface.
6.4 A large data base on performance of materials in blood as well as comparative performance of commercially available blood compatible surfaces.
6.5 Development of an infection resistant surface modification
6.6 Four new device modifications in animal testing with anticipated approval for human clinicals before 1998.

The development of broad comprehensive knowledge in methods that are effective for whatever material or device to. be used permits rapid decisions as to the cost and feasibility. Equally important is the ability to characterize and guarantee specifications called out in manufacturing process control and quality assurance claims. In the biomedical business advanced understanding of biocompatibility and development of in vitro tests that are predictive of' in vivo performance are critical for insuring product performance, and also critical in assisting in clinical protocols and follow up to assure safety and efficacy.

We conclude that we have achieved these capabilities in this project. Furthermore, they are presently in place in four development projects involving different device applications. The broad knowledge in material modification is in our opinion robust and horizontally applicable to new materials and devices coming to the market. The new technology being discussed in biomaterials is tissue engineering. Whether the new materials are biodegradable, biological, or hybrids; the know how developed in this

project. is applicable. While the efforts of this project are being turned over 'to development projects, the knowledge gained is being use in future planned research projects such as surface modification for hybrid synthetic organs and alternative new technologies for collagen and tissue fixation.

*7. Collaboration **Sought***

The partners in this project are interested in further research and collaboration via projects such as the Brite EuRam. A new larger consortium has been formed and a submission for a BE project on collagen as a biomaterial has been prepared for the 1996 submission date.

With respect to the application to medical devices of the technology developed the, BRC is primarily interested in exploitation of devices made by Medtronic. Medtronic is the largest manufacturer of implantable biomedical devices in the world, and the applications internally are numerous. Medtronic does not at this time have businesses in the areas of ophthalmic devices, orthopedic, or dental.

CSMA is primarily a service company with state of the art capability in surface analysis, as well as considerable experience and a consultant network that are capable of solving many problems in numerous industries, particularly problems in adhesives and corrosion. Contractual agreements have been made beyond this project with CSMA and the BRC. Conditions of this contract allow CSMA to provide services to all other biomedical companies.

The University of Maastricht has numerous collaborative efforts in addition to the BRC. With respect to collaboration in areas covered in this project; the BRC and RL have signed new contracts and are pursuing further applications of surface modification of biomaterials.

8. *Exploitation plans am-l anticipated **benefits***

At this time the partners have signed continuation contracts beyond this project to exploit **the** technology developed further in numerous "internal applications for devices manufactured by Medtronic. Three additional universities: Technical University of Twente, The Netherlands, Rijksuniversity Groningen, The Netherlands, and The University of Compiegne, France have signed contracts with the BRC also in continued research and development on device modifications.

The heparinized coronary stent process has been transferred to manufacturing at Kerkrade, The Netherlands. The manufacturing facility has increased staffing and is constructing additional plant space for expansion. The stent market is currently at approximately $.5 billion per year and growing at an estimated 30% annually. The BRC has increased R&D expenditures 60% for next generation stents for coronary application as well as other applications. This effort will include drug delivery.

Medtronic Corporate Ventures moved to Europe during the BE 5972 project, and this business unit has new products in development that will use surface modification technology to -provide infection resistant materials/devices. This effort has successful results to date in animal trials. This same technology is in the initial animal trials for the Tachy Pacing business unit for providing infection resistant pacemakers for implantable pacing defibrillators.

Two other business units; the Cardiopulmonary and Brady Pacing have funded projects for the development of blood compatible surfaces for cardiopulmonary bypass systems, and implantable sensors respectively.

In economic terms the immediate benefit is increased investment and employment for these European centered research and development efforts. Additional investment and employment is already taking place in the Intraventional Vascular business (stents and catheters) at the Kerkrade manufacturing center. Similar expansion is anticipated as the new applications are developed.

There is a real social benefit in providing people with more effective longer lasting medical devices with fewer complications. In the area of device associated infections it has been estimated that the annual cost to society is $1 billion. Since most infections result in removal of the device the morbidity of such procedures is most undesirable.

9. *Five keywords on the content of the project*

E43 Surface treatment
E35 Product development
E30 Polymers
E08 Coatings
A08 Bioengineering

10. *Names and addresses of the coordinator and of other partners*

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